UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/712,849	11/13/2003	Charles M. Zepp	SEPR-P01-056	9511

28120 7590 05/12/2008

ROPES & GRAY LLP
PATENT DOCKETING 39/41
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER	
POLANSKY, GREGG	
ART UNIT	**PAPER NUMBER**
1611	
MAIL DATE	**DELIVERY MODE**
05/12/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/712,849	ZEPP ET AL.	
	Examiner	Art Unit	
	Gregg Polansky	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 January 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,11,13-18,20,21 and 23-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,11,13-18,20,21 and 23-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 January 2008* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Applicants' response, filed 1/14/2008, to the Office Action mailed 9/10/2007 is acknowledged. Applicants canceled Claims 3-10, 12, 19, 22 and 30, amended Claims 81, 2, 11, 13-18, 20, 21, and 23-29, and presented arguments in response to the Office Action.

2. Claims 1, 2, 11, 13-18, 20, 21 and 23-29 are pending and presently under consideration.

3. Applicants' arguments have been fully considered and are persuasive in part. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. Claims 1, 2, 11, 13-18, 20, 21, and 23-29 are rejected under 35 U.S.C. 112, first paragraph because the specification, while being enabling for a method for **reducing** hearing impairment caused by the platinum-containing antineoplastic agent, cisplatin, by administration of 2-thiouracil prior to the cisplatin exposure, does not reasonably provide enablement for **preventing** hearing impairment caused by the platinum-containing antineoplastic agent, cisplatin, or **preventing or reducing** hearing impairment caused

by other chemical agents (*i.e.*, aminoglycoside antibiotics, ototoxic diuretics, or certain quinine-like compounds)), noise, or aging . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. This is a Scope of Enablement rejection.

The instant claims are drawn to a method of "preventing, reducing, or treating hearing impairment due to noise-induced hearing loss (NIHL), aging, or chemical-induced hearing loss (CIHL), comprising administering to a subject a compound" having a structure according to Formula I of Claim 1, between 72 hrs before and 36 hours after exposure to the hearing-impairing agent.

> The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

(1) The nature of the invention and (2) the breadth of the claims:

The claims are drawn to a method of "preventing, reducing, or otherwise treating hearing impairment due to noise-induced hearing loss (NIHL), aging, or chemical-

induced hearing loss (CIHL), comprising administering to a subject a compound" having a structure according to Formula I of Claim 1. The CIHL causing agent is an ototoxic chemotherapeutic drug selected from aminoglycoside antibiotics, platinum-containing antineoplastic agents, certain quinine-like compounds, or ototoxic diuretics. The therapeutic agent may be administered between 72 hours before to 36 hours after exposure to the agent causing the hearing loss.

According to the instant Specification, the term preventing means "to reduce the risk of occurrence of an abnormal biological or a medical event, such as hearing loss, in a cell, a tissue, a system, animal or human". The interpretation of the instant claims allows for the **reduction of risk of hearing loss or the reversal of hearing loss** caused by noise, chemicals or aging by the administration of the compounds defined by Formula I. For the method of prevention to be successful, the claimed compounds would need to be administered to anyone who may be exposed to noise or ototoxic chemicals and to everyone else (i.e., anyone who is aging).

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

The Merck Manual teaches that **age-related hearing loss is not preventable** and most other causes of hearing loss are irreversible (*see* page 6, "Prevention and Treatment", 1st and last paragraphs). For example, Goran *et al.* (U.S. Publication No. 2002/0180388) teach that **cisplatin-induced hearing loss is non-reversible** (*see* paragraph 53, lines 10-12).

Thus, it is not understood how one skilled in the art can reasonably expect that the instant compounds can be administered in order to have the "preventive" effect or to reverse hearing loss.

(5) The relative skill of those in the art:

The relative skill of those in the art of pharmacology and medicine and the unpredictability of the pharmacological and /biological arts are very high. In fact, the courts have made a distinction between mechanical elements, which function the same in different circumstances, yielding predictable results, and chemical and biological compounds, which often react unpredictably under different circumstances. Nationwide Chem. Corp. v. Wright, 458 F. supp. 828, 839, 192 USPQ 95, 105(M.D. Fla. 1976); Aff'd 584 F.2d 714, 200 USPQ 257 (5th Cir. 1978); In re Fischer, 427 F.2d 833, 839, 166 USPQ 10, 24(CCPA 1970). Thus, the physiological activity of a chemical or biological compound is considered to be an unpredictable art. Likewise, the physiological or pharmaceutical activity of treating or preventing retinopathy, particularly retinopathy of undefined etiology, is an unpredictable art.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The Specification has provided guidance and a working example for a method of **reducing** hearing impairment caused by the platinum-containing antineoplastic agent, cisplatin, by administration of 2-thiouracil **prior** to the cisplatin exposure. The Specification provides *in vivo* data demonstrating a reduction of hearing loss in rats

treated with 2-thiouracil prior to administration of cisplatin. The presentation of the data in the provided figures makes it is impossible to determine whether any of the other treatments displayed in the figures had any significant protective effects.

However, the Specification does not provide guidance or a working example for a method of **preventing** hearing impairment caused by the platinum-containing antineoplastic agent, cisplatin, or **preventing or reducing** hearing impairment caused by other chemical agents (*i.e.*, aminoglycoside antibiotics, ototoxic diuretics, or certain quinine-like compounds)), noise, or aging. There is no guidance or working example for preventing, reducing or reversing hearing impairment when treatment is given **after** patient exposure to the causative agent. The most extreme example of the deficiencies of the claims is that of the method of preventing or reducing hearing impairment caused by aging. The Merck Manual teaches that age-related hearing loss affects everyone and begins some time after the age of 20 (*see* "Age", pages 1-2). Therefore, since age-related hearing loss is irreversible (*supra*), the administration of the claimed compounds would need to begin before any loss occurs and must continue indefinitely. Since most chemical agents have potentially deleterious effects, lifetime treatment with such a compound, particularly one that has not been demonstrated to be beneficial for the treatment of age-related hearing loss, would inadvisable.

Although the Applicants may serve as their own lexicographer, the definition of "prevents" recited by the Applicants in the Specification (page 5, lines 16-19), is repugnant to one skilled in the art and is therefore not acceptable.

(8) The quantity of experimentation necessary:

The amount of guidance or direction needed to enable the invention is inversely related to the degree of predictability in the art. *In re Fisher*, 839, 166 USPQ 24. Thus, although a single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements, in cases involving unpredictable factors, such as most chemical reactions and physiological activity, more teaching or guidance is required. *In re Fisher*, 427 F.2d 839, 166 USPQ 24; *Ex Parte Hitzeman*, 9 USPQ 2d 1823. For example, the Federal Circuit determined that, given the unpredictability of the physiological activity of RNA viruses, a specification requires more than a general description and a single embodiment to provide an enabling disclosure for a method of protecting an organism against RNA viruses. *In re Wright*, 999 F.2d 1562-63, 27 USPQ2d 1575. The Office maintains a very high standard of enablement for claims drawn to a methods of prevention.

As discussed above, considering above factors, especially the "sufficient working examples", "the level of skill in the art", "the relative skill and the unpredictability in the pharmaceutical art", "breadth of the claims" and "the chemical nature of the invention", one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the claimed compounds for the claimed methods of prevention.

6. Applicants argue there is guidance and working examples in the Specification for the reduction or treatment of hearing loss caused by cisplatin, thus providing sufficient

enablement for the treatment or reduction of hearing loss caused by "anything that invokes this same destructive mechanism". The Examiner disagrees. Lines 24-28 of page 2 states "While the efficacy of 2-thio-nitrogen-containing compounds disclosed herein may be due to their antioxidative properties *vis-à-vis* reactive oxygen species generated by, for instance, an aminoglycoside antibiotic or a platinum-containing antineoplastic agent, the efficacy may also be due to another mechanism, such as inhibition of nitric oxide synthetase by the otoprotective compounds disclosed in the present invention." This statement is interpreted as disclosing the mechanism for the efficacy of 2-thio-nitrogen-containing compounds has yet to be determined. No guidance or data are provided for any of the other claimed causes of hearing loss (e.g., age, noise, other ototoxic chemical). Considering the Wands factors, as discussed above, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the claimed compounds for the claimed methods of prevention.

Claim Rejections - 35 USC § 102

7. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

8. Claims 21 and 23-28 are rejected under 35 U.S.C. 102(b) as being anticipated by Paschkis et al. (Science, Vol. 114, pages 264-265).

The claims are drawn to a pharmaceutical dosage form of compounds represented by formula I, as recited in Claim 21.

Paschkis et al. teach 2-thiouracil pellets, implanted subcutaneously or dissolved in drinking water and administered orally. See page 264, right column, 2nd, 3rd, and 4th paragraphs from the bottom.

The dosage amounts recited in Claims 25-28 read on intended use; however, intended use confers no patentable weight to composition claims. *In re Hack*, 114 USPQ 161.

Conclusion

9. Claims 1, 2, 11, 13-18, 20, 21 and 23-29 are rejected.

10. No claims are allowed.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregg Polansky whose telephone number is (571)272-9070. The examiner can normally be reached on Mon-Thur 9:30 A.M. - 7:00 P.M. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gregg Polansky/
Examiner, Art Unit 1611

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614